

REMARKS**Claim Amendments**

Claim 4 has been amended to recite "comprising a flexed silicon oxide coated polyester film." Claim 9 has been amended to recite "comprising a flexed silicon oxide coated polyester film." Support for these amendments is found on page 7, lines 5-27, and on page 34, lines 8-15, which describe the use of a silicon oxide material using a TIROMAT® sealing apparatus.

Claims 5 and 10 have been amended to agree from Claims 4 or 9, respectively. In particular, Claims 5 and 10 have been amended to recite "deoxygenated" hemoglobin blood substitute."

Claims 5, 6, 10, and 11 have also been amended to correct claim dependency.

No new matter has been added.

Applicants' Claimed Invention

Applicants claim a method for preserving a deoxygenated hemoglobin blood substitute and a preserved deoxygenated hemoglobin blood substitute. The method comprises maintaining the deoxygenated hemoglobin blood substitute in an oxygen barrier film overwrap that includes a transparent laminate material and a foil laminate material, wherein the transparent laminate material includes a flexed silicon oxide layer. The preserved deoxygenated hemoglobin blood substitute comprises a deoxygenated hemoglobin blood substitute contained within a primary package and oxygen barrier film overwrap that includes a transparent laminate material and a foil laminate material, wherein the transparent laminate material includes a flexed silicon oxide layer, within which the deoxygenated hemoglobin blood substitute and the primary package are sealed, thereby preserving the deoxygenated hemoglobin blood substitute. The foil laminate is formed to define at least one chamber, the packaged deoxygenated hemoglobin is placed in the chamber, and the transparent laminate is heat sealed to the foil laminate forming an oxygen barrier overwrap containing the packaged deoxygenated hemoglobin blood substitute.

Advantages of Applicants' Invention

Applicants' method for preserving deoxygenated hemoglobin and the preserved deoxygenated hemoglobin of the invention can be practiced without loss of barrier properties of the silicon oxide layer which is otherwise likely to occur during fabrication of the overwrap (page 2, lines 31-33; page 7, lines 20-27 and page 34, lines 8 -15). Importantly, the preserved deoxygenated hemoglobin blood substitute remains stable at room temperature for periods of a year or more (see page 4, lines 23-25 and page 34, line 8 through page 35).

As a result of Applicants' invention, commercial scale production of preserved deoxygenated hemoglobin is possible using transparent, silicon oxide-containing oxygen barrier laminates without significant loss of barrier properties of the laminate. The preserved deoxygenated hemoglobin blood substitute of the invention includes a blood substitute contained within a package with at least one clear face, eliminating the need for a label on the overwrap, because a label on the primary package can be viewed through the transparent component. Furthermore, visual inspection of the product for quality, as evidenced by color, can be conducted without breaching the seal of the overwrap.

Declaration of Dr. Robert A. Houtchens

In the U.S. Serial No. 09/349,290 to which this applications claims priority as a continuation, Robert A. Houtchens, Ph.D., Associate Director, Process Development, of Research and Development at Biopure Corporation, made a Declaration under 37 C.F.R. § 1.132. A copy of the original Declaration is enclosed with this Amendment.

In the Declaration, Dr. Houtchens stated that the TIROMAT® sealing apparatus inherently flexes the silicon oxide layer during overwrapping of a deoxygenated hemoglobin blood substitute. Dr. Houtchens stated that Dodrill teaches that the barrier data for silicon oxide containing laminates are highly variable because of the sensitivity of the silicon oxide material to flexing, and that the data are not representative of actual package performance. Dr. Houtchens further stated that based on the teachings of Dodrill, one of ordinary skill in the art would not expect to be able to preserve a deoxygenated hemoglobin blood substitute comprising maintaining the deoxygenated hemoglobin blood substitute in an oxygen barrier film overwrap that includes a transparent laminate material that includes a flexed silicon oxide layer.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nho, *et al.* in view of Dodrill. The Examiner stated that “[t]he claims are drawn to method of preserving hemoglobin in an oxygen-impermeable container. The container is an oxygen barrier foil over wrap and further comprises a foil laminate material and a polymer layer. The Examiner described the teachings of Nho, *et al.* and Dodrill and concluded that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a blood substitute as disclosed by Nho, *et al.* and then store the blood substitute in a storage container as disclosed by Herbert al. (sic Dodrill) because the bags would keep the hemoglobin in the deoxy-state, due to the low oxygen permeability of the films, and thereby increasing the storage life of ready to use hemoglobin.

Nho, *et al.* teach a method for producing deoxygenated, chemically modified hemoglobin. Nho, *et al.* teach the storage of the final product in a gas-impermeable blood bag (Col. 16, lines 14-16). According to Nho, *et al.*, the deoxygenated, modified hemoglobin may be stored at 4° C and may be warmed for immediate transfusion (Col. 17, lines 26-34). Furthermore, Nho, *et al.* teach that the deoxygenated, modified hemoglobin is stable for short periods at 37° C.

There is no teaching or suggestion in Nho, *et al.* for an oxygen barrier film overwrap that includes a transparent laminate material and a foil laminate material, wherein the transparent laminate material includes a flexed silicon oxide layer. Further, Dodrill does not remedy the deficiencies of Nho, *et al.*, taken either separately or in combination.

Dodrill does not teach or suggest preserving a deoxygenated hemoglobin blood substitute by using any of the materials disclosed therein. Furthermore, as stated in the Declaration under 37 C.F.R. § 1.132 by Dr. Robert A. Houtchens, Dodrill teaches that the barrier data for silicon oxide containing laminates are highly variable because of the sensitivity of the silicon oxide material to flexing, and the data are not representative of actual package performance. According to Dr. Houtchens, Dodrill teaches that the silicon oxide film with the highest barrier properties described therein does not reliably maintain barrier properties under actual packaging conditions. In the Declaration, Dr. Houtchens stated that based on the teachings of Dodrill, one of ordinary skill in the art would not expect to be able to preserve a deoxygenated hemoglobin blood

substitute comprising maintaining the deoxygenated hemoglobin blood substitute in an oxygen film overwrap that includes a transparent laminate material that includes a flexed silicon oxide layer.

As described above, the Applicants' invention provides the advantage of being able to use transparent laminate material in mechanical packaging devices to rapidly package the deoxygenated hemoglobin without loss of barrier properties. Silicon oxide-containing films are known to be sensitive to flexing and stress with potential loss in barrier properties due to the cracking or introduction of discontinuities in the silicon oxide layer caused by flexing of the silicon oxide layer. Based on Applicants' invention, one can use the silicon oxide material in mechanical packaging devices, where the material is flexed over a number of rollers, without loss of barrier properties and without requiring special handling of the package by the manufacturer or end user. Furthermore, by having at least one clear face on the overwrap, it is not necessary to have a second label on the outside of the overwrapped package.

As discussed above, Applicants have amended the claims to state that silicon oxide layer employed by the method of the invention is flexed. Robert A. Houtchens, Ph.D., who is a named inventor, stated in a Declaration under C.F.R § 1.132, that overwrapping of a deoxygenated blood substitute by use of a TIROMAT® automated sealing apparatus, as described in the specification, flexes the silicon oxide layer employed in the overwrap. Therefore, flexing of the silicon oxide layer is inherent in at least one method employed by the method of the specification to overwrap and thereby preserve the deoxygenated hemoglobin blood substitute according to the claimed method. Dr. Houtchens also stated in his Declaration that it would not be obvious to one of ordinary skill in the art to overwrap a deoxygenated hemoglobin blood substitute with a transparent laminate material that includes a flexed silicon oxide layer.

The combination of Nho, *et al.* and Dodrill fails to render Applicants' claimed invention obvious because there is no teaching or suggestion in the cited references, taken separately or in combination, that deoxygenated hemoglobin can be preserved as claimed. None of the cited references, separately or in combination, teach the use of a foil laminate material together with a transparent, flexed silicon-oxide containing laminate to form an overwrap. Furthermore, there is no teaching or suggestion in the cited art either separately or in combination of shaping the foil laminate as claimed. Therefore, Claims 4-6 and 9-11 are non-obvious over Nho, *et al.*, in view

of Dodrill under 35 U.S.C. § 103. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

Claims 1-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-14 of U.S. Patent No. 6,610,832. Claims 1-28 are also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-15 of U.S. Patent No. 6,271,351. A Terminal Disclaimer over U.S. Patent No. 6,610,832 and over U.S. Patent No. 6,271,351 is being filed concurrently herewith.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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